DOCTOR DEGREE

CLINICAL, HISTOLOGICAL AND IMMUNOHISTOCHEMICAL STUDY OF PERIODONTITIS WITH GINGIVAL HYPERTROPHY IN PATIENTS WITH DIABETES MELLITUS

- ABSTRACT -

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INTRODUCTION

Diabetes mellitus consists of a group of diseases characterised by abnormally high blood glucose levels. The two main types of diabetes mellitus are type 1 or insulin-dependent diabetes mellitus (IDDM) and type 2 or non-insulin-dependent diabetes mellitus (NIDDM). Type 1 diabetes usually manifests in childhood or adolescence, and as the name (IDDM) implies, the patients require exogenous insulin because of the destruction of insulin-producing β cells in the pancreas by autoimmune reactions. The prevalence of type 2 diabetes begins to rise in early middle age and increases along with age.

Exogenous insulin may not be a necessity for these patients, because insulin production is less or not at all decreased in type 2 compared to type 1 diabetes, and the basic reason for metabolic disturbance is insulin resistance [1,2].

The oral health of patients with diabetes has been widely investigated. This research has mainly focused on periodontal diseases and dental caries, which can be considered as national diseases because of their high prevalence rates. Most of the studies have compared patients with diabetes to controls, but their results have been somewhat contradictory [3]. These results, however, have indicated that diabetes can be seen as a risk factor for oral diseases, especially periodontal diseases [4,5]. The inconsistency of the results may relate to the fact that diabetes is a very complex multiform disease, and the study populations may therefore be very heterogeneous. Most evidently, not all patients with diabetes are at equal risk for oral complications, and some variation is apparently related to the differences in the diabetic status of the patients.

Despite these efforts, there is not yet any agreement as to how the diabetic status should be evaluated with respect to the risk for oral diseases. An ability to identify the diabetic patients at a higher risk for oral complications would benefit the dental care of patients with diabetes, as the prophylaxis and treatment could then be targeted more efficiently to the risk subjects among the increasing number of diabetic patients.

Moreover, there is evidence to suggest that treatment and prophylaxis of oral infections could benefit the maintenance of good metabolic control of diabetes [6]. The present studies were conducted to find out a suitable way to assess the diabetic status of patients, which could help both the dental and the medical professionals responsible for care of the treatment of patients with diabetes, to identify the patients most urgently in need for dental care.

Diabetic organ complications

Vascular complications of diabetes occur in both micro- and macrovascular vessels. Microvascular complications include retinopathy, nephropathy and neuropathy. Macrovascular complications comprise peripheral vascular disease and cardiovascular complications, such as ischemic heart disease and hypertension. These are all chronic illnesses which take 10–20 years to manifest. One of the most important factors in the pathogenesis of diabetic complications is the metabolic milieu of the diabetic patients, the main causative factor being hyperglycaemia [7]. The severity of complications is modified by genetic factors, since many of the diabetic patients do not develop complications even when their glycaemic control is not optimal [8].

Retinopathy is common in both type 1 and type 2 diabetes, and its prevalence is strongly related to the duration of diabetes. In patients with type 1 diabetes, the first changes in the small vessels of the retina may appear after 4–7 years of diabetes. About 20–30 percent of patients with type 2 diabetes already have retinopathic changes at the 19 time when their diabetes is diagnosed, presumably because type 2 diabetes may go undiagnosed much longer than type 1 diabetes. The etiology of retinopathy includes hyperglycaemia-associated biochemical, anatomical and functional changes.

Nephropathy arises from glomerulosclerosis, which is characterised by glomerular basement membrane thickening and arteriosclerosis of small arterioles. The mechanisms proposed to induce glomerulosclerosis include hyperglycaemia, a hyperfiltration-related increase of glomerular pressure and increased blood viscosity. Nephropathy may culminate in uraemia and, in fact, most of the hemodialysis patients and the patients receiving renal transplants, have diabetes. [9-11].

High blood pressure manifests along with the progression of nephropathy: in patients with microalbuminuria, blood pressure gradually increases. Hypertension contributes notably to the progression of renal disease and retinopathy, and early antihypertensive treatment is crucial. Hypertension is more often part of the metabolic syndrome that includes glucose intolerance, insulin resistance, obesity, dyslipidemia and coronary heart disease. Due to arteriosclerosis, hypertension and dyslipidemias, diabetic patients are also at a higher risk for decreased peripheral blood flow, ischaemic heart disease and other cardiovascular problems compared to nondiabetic subjects. Abnormal fibrinolysis and altered platelet function also increase the risk of macrovascular complications among patients with diabetes [12-15].

The third microangiopathic complication of diabetes is neuropathy, and the main histological finding is thickening of the basement membranes of nerve sheets and the capillaries that supply blood to the nerves. Reduced nerve perfusion is an important factor in the etiology of neuropathy, but many metabolic changes, such as an activated polyol pathway, non-enzymatic glycosylation and increased oxidative stress, for example, have recently been
related to poor control of diabetes [22-26].

**Metabolic control of diabetes**

Large follow-up studies have shown that good glucose control may prevent or delay the manifestation of complications despite the long duration of the disease [17-19]. The evaluation of the level of metabolic control of diabetes is mainly based on the monitoring of blood glucose levels.

Erythrocytes are freely permeable to glucose. In cells, glucose attaches to the free amino ends of haemoglobin molecules, and this process, called non-enzymatic glycosylation, causes glycosylated haemoglobin to be formed directly proportional to the blood glucose concentration. As the average erythrocyte life span is about 120 days, glycosylated haemoglobin levels give information on the mean average blood glucose levels over the past 2 to 3 months. Two main fractions of glycosylated haemoglobin, HbA1 or HbA1c, are commonly used in diabetes monitoring. The normal range for HbA1c is 4–6 percent, and the values for HbA1 are about two percentage points higher, as HbA1c is a smaller part of the HbA1 fraction. According to generally accepted guidelines in the clinical monitoring of diabetic patients, diabetes is considered to be well controlled if the HbA1c levels are 21 below 7.5%, and moderately controlled if the HbA1c levels vary between 7.5–8.5%.

Values from 8.6 to 10.0% indicate poor control of the disease, and values over 10% are considered alarmingly high.

Although carbohydrate metabolism plays a central role in the pathophysiology of diabetes, the treatment aims at normalising blood glucose levels and treatment monitoring is mainly based on blood glucose levels, protein and lipid metabolisms are also affected [20,21]. Other metabolic disorders are not, however, monitored so often and on such a routine basis as blood glucose or glycosylated haemoglobin levels. Different ways to evaluate the level of metabolic control can be used concomitantly to give complementary information. However, the availability of glycosylated haemoglobin measurements has made it possible to evaluate the role of long-term glucose control in developing diabetic complications, and has been adopted in dental studies as well.

**Diabetes-related tissue alterations**

Diabetes is known to lower the host’s resistance to infections and to impair wound healing. Insulin is necessary for glucose to enter cells and to provide a source of energy, for the uptake of amino acids to synthesise proteins, and for the inhibition of adipose tissue lipolysis. If insulin is not adequately supplied, basic cell functions in the body will consequently be disturbed. Signs of deterioration of the first-line host defence against microbes, i.e. impairment of PMN cell function with abnormalities of adherence, chemotaxis, phagocytosis and intracellular killing, are well known. Defects in PMN cell functions have been shown to be related to poor control of diabetes [22-26].

Changes in the turnover and structure of collagen, the main component of the extracellular matrix, such as decreased synthesis, increased degradation of newly synthesised collagen and decreased solubility of mature collagen, have been demonstrated in both human and animal diabetes studies. In diabetes, connective-tissue collagen is less soluble and more resistant to digestion, and the thermal rupture time and mechanical strength are also increased [27-30]. The increased thickness of basement membranes, especially capillaries, in diabetes is well documented. Biochemical studies have shown that basement membranes in diabetes include excess amounts of type IV collagen, the main component of basement membranes, and decreased amounts of proteoglycans, both of which changes decrease the permeability of capillaries and disturb leukocyte diapedesis, oxygen diffusion, nutrition and metabolic waste removal.

Tissue oxygenation is further impaired by the decreased ability of glycosylated haemoglobin to carry oxygen. Furthermore, hyperglycaemia increases blood viscosity, reduces erythrocyte deformability and increases platelet aggregation, which all cause blood flow abnormalities and, furthermore, platelet aggregation is followed by the release of serotonin and lysosomal enzymes.

Non-enzymatic glycosylation has recently attracted increasing interest as a crucial pathophysiologic event behind all these hyperglycaemia-related alterations and in the pathophysiology of the development of diabetic complications. Proteins and lipids exposed to aldose sugars go through reactions which are not enzyme-dependent, and generation of reversible Schiff bases or Amadori products take place. Later, through further molecular rearrangements, irreversible advanced glycosylation end products (AGEs) are formed [31,33]. This process also takes place during normal ageing, but in diabetes their formation is accelerated to an extent related to the level and duration of hyperglycaemia. The potential pathophysiological significance of AGEs is associated with their accumulation in plasma, cells and tissues and their contribution to the formation of cross-links, generation of reactive oxygen intermediates and interactions with particular receptors on cellular surfaces. AGEs have direct effects on the host response by affecting tissue structures, e.g. by increasing collagen cross-links, which is followed by changes in collagen solubility and turnover. Thickening of basement membranes is partly due to glycosylation of membrane proteins or entrapment of glycosylated serum proteins into basement. Specific cell-surface receptors for the recognition of AGEs were first found on mononuclear phagocytes, and AGEs were observed to attract and retain mononuclear phagocytes [34-36].

Later, these receptors have been identified on lymphocytes, endothelial cells and smooth muscle cells as well as on other cellular systems that participate in both normal tissue remodelling and tissue damage. AGEs are bound to the specific cell surface receptors for AGEs, within which family of
receptors RAGE is the most well defined and resembles macrophage scavenger receptors (MSR). This interaction results in oxidant stress of the target cells, inducing production of different patterns of cytokines and growth factors, depending on the type of cells involved. Excess production of growth factors and cytokines plays an essential role in both micro- and macrovascular alterations. AGEs, by themselves, appear to generate reactive oxygen intermediates and the interaction between AGE and RAGE further induces production of intra- and extracellular oxidants.

Oxidative modifications of lipoproteins, in turn, accelerate atherogenesis. Free oxygen radicals cause tissue destruction directly and exaggerate the constructional tissue destruction because activated monocytes produce proinflammatory cytokines, such as IL-1β, IL-6 and TNF-α. Based on what has been said above, it is evident that AGEs can interact with cell functions, tissue remodelling and inflammatory reactions in several different ways.

In conclusion, hyperglycaemia, either directly or through AGE formation, causes various structural and functional modifications of cells as well as qualitative and qualitative alterations of the extracellular matrix, which may all alter tissue homeostasis and modify the host response even in periodontal and other oral tissues.

**Oral health in relation to metabolic control of diabetes**

**Periodontal diseases**

Evaluation of metabolic control was quite difficult until in the 1980s, when glycosylated haemoglobin values became available for monitoring metabolic control. Gingival bleeding was observed to increase as the level of metabolic control deteriorated [37-39].

With respects to pocketing and alveolar bone loss, the differences were not so obvious; however, well controlled subjects had better periodontal conditions than controls, and a trend towards severe periodontal disease in moderately and poorly controlled subjects compared to well controlled ones was obvious [39-41].

Although the role of poor control of diabetes as a predisposing factor for periodontal disease has been reported in several studies even thereafter, contradictory results are also numerous. In younger study populations, i.e. children and adolescents, the level of metabolic control has been mainly studied in relation to gingival inflammation. In some studies it was found more gingival inflammation in poorly controlled children than in well controlled ones before puberty. The increase of gingival inflammation during puberty and along with age was more obvious than the effect of poor control during and after puberty, however. In a couple of studies, more gingival inflammation in poorly controlled diabetic children compared to healthy controls has been reported, but the differences between well and poorly controlled subgroups were less obvious. The absence of an association between gingivitis and glycosylated haemoglobin values in young study populations has been reported in many. Quite a few studies on children and adolescents have included pocket or attachment loss measurements in their protocols [43-45].

Mostly, however, no differences in the extent of deepened pockets or attachment loss between well and poorly controlled young diabetic patients have been found.

Infections are generally known to disturb the metabolic control. A couple of studies have explored whether a reduction of periodontal infection has any effect on the level of glucose control. In one study slight evidence to suggest that gingival inflammation might impair the glucose control was obtained, as a good response to treatment was accompanied by a decline of HbA1c levels, while no change in the HbA1c values was seen in those who did not respond favourably to the treatment [46]. Grossi et al. studied poorly controlled type 2 diabetic patients with periodontitis who were randomised into five treatment groups. All underwent scaling and curettage combined with different combinations of antimicrobial treatment. Three months and six months after therapy, all groups showed a favourable response, i.e. a reduction of plaque scores, gingival scores and mean probing depth. From baseline to three months, a significant reduction of HbA1c values was observed, but only in the groups who received systemic doxycycline therapy [47,48].

The change in fasting blood glucose levels, however, was not so obvious, and the ability of doxycycline to prevent non-enzymatic glycosylation might have reduced HbA1c values. At six months, HbA1c levels returned to baseline values, but no recurrence of periodontal infection was seen from three to six months. Based on these results, the authors concluded that the control of periodontal infection has favourable effect on diabetes management. In another study, no changes in HbA1c values were observed four months after non-surgical periodontal treatment. It is noteworthy, however, that the diabetic subjects of that study already had good metabolic control at baseline.

In most cases, local etiologic factors have not been different in the various subgroups based on the level of metabolic control, with a few exceptions: higher plaque or calculus scores in poorly controlled subjects compared to well controlled. No microbiological or antibody assessments have revealed any significant associations between the microbiological composition of plaque and the level of glucose control. Mandell et al. [49] had subjects with poorly controlled long-duration diabetes, and the high levels of organisms found in subgingival samples of diseased sites were similar to those associated with periodontal destruction in other patient populations. Sastrowijoto et al. reported a group of well controlled diabetic patients with HbA1c values equal to or lower than 7.7% and poorly controlled subjects with HbA1c values of 9.9% or higher [50,51]. The periodontopathogens found were the same as those commonly seen in adult periodontitis, i.e. *A. actinomycetemcomitans* and *Bacteroides* species. *Capnocytophaga* species, which have previously been suggested to be related to...
periodontitis of diabetic subjects [52], were found to be present in low numbers independently of the level of metabolic control.

II. PERSONAL CONTRIBUTIONS

The aim of our study was to appreciate the periodontal disease evolution degree in studied patients with DM, in order to create a utile data base for detection of this pathology in diabetic patients. The histological and immunohistochemical studies followed the histopathological changes reveal at gingival epithelium level, profound and superficial chorion. We have been interested in vessels, collagen and inflammatory infiltrate alterations.

The future research lines in dental medicine should be focused on periodontal disease potential over systemic evolution influence. The role of periodontal treatment should be guided towards specific infections eradictions.

1. CLINICAL STUDY

MATERIAL AND METHOD

We examined 117 patients diagnosed with DM in Diabetes Clinic of Emergency County Clinical Hospital from Craiova and in Parodontology Department of Faculty of Dental Medicine in Craiova. The periodontal status evaluation was undertaken using general and local clinic examination and also paraclinical investigations.

a. For the clinical exam we used and tested: inspection, palpation, periodontal measurements, dental mobility, gingival bleeding, integrity and forms of arcades, irritative local factors,

b. Paraclinical exams: plaque index, Papilar bleeding index - Saxen și Muhlemann, gingival index, periodontal attachment, radiology, periodontal pockets depth, dental mobility.

We was also interested in DM history, glucose and glycated hemoglobin levels.

RESULTS AND DISCUSSIONS

Clinical results from our study correspond to literature data that confirm the role of DM in periodontal disease pathogeny, severity and evolution. [53].

Generally patients with DM have a higher prevalence of periodontal disease compared to the healthy population [54]. On the contrary, there are authors who reported that there is no direct relationship between the two diseases [55-57].

We noticed that the periodontal status in well-controled DM is similar to nondiabetic patients. Moreover, patients with precarious metabolic control have severe gingival inflammations, great attachment losses, bone loss [58].

Studies on diabetic patients are numerous. The periodontal disease has been discovered as common and more severe in patients with DM then in controls [59-61]. Thorstensson și Hugoson [62] reported that periodontal disease begins earlier for diabetic patients than in controls and the differences are more evident in group of 40 and 49 years old. There were no major differences in patients 50-59 and 60-69 y.o.

we found in our study that a bad metabolic control stimulates gingival inflammation and bleeding in the presence of bacterial plaque. We diagnosticated more periodontitis than gingivitis. As a conclusion, a rigorous prevention and an efficient periodontal treatment in DM patients with a bad metabolic control can prevent the severe evolution of periodontal disease.

We learned from the literature that DM influences the risk for periodontal inflammation and destruction. It is not necessary that a diabetic patient should have gingivitis or periodontitis. The diabetic metabolic metabolism seems to play an important role in periodontal disease onset. The prevalence and severity of periodontal signs depend on the metabolic control of DM.

Patient61 years old, masculine, urban, DM type 1 and aggressive chronic periodontitis

Figure no. 1
Clinical aspect

Figure no. 2
HbA1c value
CONCLUSIONS FOR CLINICAL STUDY

We noticed that the studied patients generally presented a long term DM evolution. We can not conclude that the DM long evolution is the cause for periodontal disease severity, but it can influence the aggressive periodontal signs onset if in presence of a bad metabolic control and a poor hygiene.

The influence factors for a severe periodontal evolution are bacterial plaque and dental calculus.

The most frequent periodontal diseases were chronic moderate and severe periodontitis in patients of 40-55 years old, no matter of the DM type.

Gingival bleeding was common, at high levels, also the gingival inflammation intensity was related to the systemic state and local factors as dental plaque and calculus. The gingival inflammation was cantonated especially in the front teeth. The gingival overgrowth was moderate, with specific sessile and pediculate pollips and high gingival bleeding.

Patients with aggressive periodontitis had frequent deep periodontal pockets, dental mobility of grade 2. The radiography indicated important horizontal and vertical bone losses, with an interdental starting point.

HbA1C high level were correlated with the aggressive forms of periodontal disease. HbA1C value is a better indicator for a long term metabolic control of DM compared to the glucose level.

2. HISTOLOGICAL AND IMMUNOHISTOCHEMICAL STUDY

MATERIAL and METHOD

The studied material was represented by gingival tissue fragments gathered after the extractions of irretrievable teeth from 68 patients diagnosed with DM in the Diabetes and Nutrition Clinic of the Emergency Clinical Hospital in Craiova. Our study took place during 2006 and 2008. All the patients selected for the present study accused specific clinical symptoms of the periodontal disease by the moment of our investigation: gingival inflammation, gingival bleeding and recession, dental mobility or loss. We selected 30 patients (15 with DM type 1 and 15 with DM type 2) for the immunohistochemical study.

In addition to the specific symptoms, another including criteria for our study was the lesion macroscopic aspect. Therefore patients with macroscopic aspects suggestive for different types of periodontal disease associated to the DM were accepted for our research (gingival sessile and pediculated overgrowth, gingival bleeding, great loss of periodontal attachment with deep periodontal pockets).

The mucosal fragments gathered after the extractions of irretrievable teeth were immediately fixed in 10% neutral formalin solution and then processed through the usual technique of paraffin inclusion. This technique is indicated for both histological and immunohistochemical exams in order to preserve the antigenicity of the different structures.

There have been used the hematoxylin eosine and trichromic Goldner-Szeckeli stainings for the histological study and concentrated antigens of DAKO Cytomation for the immunohistochemical study (CD31, CD34, FVIII in cocktail; CD20 and CD45RO).

The purpose of this study was to go through a histological and immunohistochemical analyze of the gingival epithelium and chorion changes (inflammatory infiltrate, blood vessels, collagen fibres) from gingival tissue in patients with diabetes mellitus and periodontal disease.
RESULTS

Figure no. 4
Patient with less than 10 years DM, vasodilatation and neoforming vessel, HE stain ob. 20x

Figure no. 5
Patient with less than 10 years DM, vasodilatation and unregulated vessel, trichromic GS stain ob. 20x

Figure no. 6
CD31, CD34 and F VIII immunostaining in a patient with DM of less than 10 years evolution, many subepithelial vessels, hyperemia (ob. 10x)

Figure no. 7
Patient with less than 10 years DM, intense inflammatory infiltrate, diffuse pattern into the chorion, HE stain ob. 20x

Figure no. 8
Patient with more than 10 years DM, discrete inflammatory infiltrate, diffuse pattern into the chorion, HE stain ob. 20x

Figure no. 9
CD45RO immunostaining in a patient with DM of less than 10 years evolution, intense intra and subepithelial T lymphocyte infiltrate (ob. 10x)

Figure no. 10
Collagen dissociation by inflammatory infiltrate, trichromic GS stain ob. 10x

CONCLUSIONS OF THE HISTOLOGICAL AND IMMUNOHISTOCHEMICAL STUDY

Patients with DM and periodontitis presented major histological alterations of the gingival epithelium and also an inflammatory infiltrate with a variable morphology depending on the DM evolution, metabolic control and oral hygiene.

The parodontopatic patients associate hypertrophy of gingival epithelial modifications in many cases with epithelial permeability and the presence of intraepithelial inflammatory cells.

Patients with a long evolution of DM present parakeratosis as a defense in front of the bacterial plaque.

Blood vessels in gingival chorion of patients with DM have early onset and are represented by the endothelial cell turgescency associated with deregulated lumen in patients with DM of less than 10 years evolution and thin lumen and thick walls vessels in patients with DM and more that 10 years evolution. The MMVD in gingival chorion immunohistochemically detected is higher in patients with a DM less than 10 years compared to the more than 10 years. However there were no statistical differences between the 2 groups.
The periodontitis diabetic inflammatory infiltrate was polymorph, plasmocyte predominant in patients with aggressive periodontitis and a poor metabolic control of the DM, and PMN predominant in patients with clinical periodontal abscesses, the lymphocyte always being constant.

The lymphocyte inflammatory infiltrate was mostly diffuse into the gingival chorion of the diabetic patients no matter of the DM evolution. The nodular pattern was characteristic for the patient with a less than 10 years evolution DM. The lymphocyte inflammatory infiltrate intensity was higher in patients with periodontitis and less than 10 years evolution DM compared to the patients with more than 10 years evolution DM.

CD45RO positive T lymphocytes were more numerous than CD20 positive B lymphocytes and they were present gingival intra and subepithelial in all diabetic patients, regardless of the DM evolution.

The extracellular matrix of gingival chorion is deeply damaged in patients with periodontitis and DM, with a predominance of destructive collagen lesions in DM of less than 10 years.


